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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/746,567	12/21/2000	Angel Cebolla Ramirez	AM-00106.P.I-US	1592

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[REDACTED] EXAMINER

SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	[REDACTED]

DATE MAILED: 01/29/2003

| 2

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/746,567	CEBOLLA RAMIREZ ET AL.
	Examiner Daniel M Sullivan	Art Unit 1636

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 08 November 2002.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 42 and 47-81 is/are pending in the application.
- 4a) Of the above claim(s) 42 and 47 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 43-81 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 08 November 2002 is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input checked="" type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

This Non-Final Office Action is a response to the “Response to Office Action” filed 8 November 2002 (Paper No 11) in reply to the Non-Final Office Action mailed 2 July 2002 (Paper No. 7). Claims 14, 17 and 43-46 were considered in Paper No. 7. Claims 17-41 and 43-46 were canceled and claims 48-81 were added in Paper No. 11. Claims 42 and 47-81 are pending in the application. Claims 42 and 47 were withdrawn from consideration in Paper No. 7. Claims 48-81 are presently under consideration.

Response to Amendment

Priority

Receipt of certified copies of the priority documents is acknowledged.

Oath/Declaration

Receipt of a corrected Declaration is acknowledged.

Drawings

The drawings filed on 11 November 2002 are acceptable subject to correction of the informalities indicated on the attached “Notice of Draftperson’s Patent Drawing Review,” PTO-948. In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

35 U.S.C. § 112, first paragraph, enablement

Rejection of claims 17-41 and 43-46 under 35 U.S.C. § 112, first paragraph, as lacking enablement for the full scope of the claims is rendered moot by the cancellation of the claims. Limitation of newly added claims to a cascade genetic circuit provided *in vitro*, in gram negative bacteria or in cultured eukaryotic cells obviates the rejection of record in Paper No. 7.

35 U.S.C. § 112, second paragraph

Rejection of claims 21, 40, 41 and 43-46 under 35 U.S.C. § 112, second paragraph, as indefinite is rendered moot by the cancellation of the claims in Paper No. 11.

Rejection of the newly added claims for the reasons of record regarding claims 40, 41, 43, 45 and 46 is obviated by the limitation of the claims to a cascade genetic circuit provided *in vitro*, in gram negative bacteria or in cultured eukaryotic cells.

Applicant argues persuasively in Paper No. 11 that new claim 52 is not indefinite.

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 48-81 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed.*” (See page 1117.) The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116).

The claims of the instant invention are directed to a cascade genetic circuit comprising a plurality of transcriptional regulators wherein one of said transcriptional regulators is under the control of a second transcriptional regulator and at least two of said transcriptional regulators are responsive to an inducer. Further, the cascade genetic circuit must comprise a target promoter that is responsive to a transcriptional regulator that is under the control of a second transcriptional regulator. Claims are also directed to a host cell comprising the cascade genetic circuit and methods of using the cascade genetic circuit. The claims thus encompass products and methods of using a very broad and functionally diverse genus of cascade genetic circuits made up of species which are distinguished by the identity and function of the transcriptional regulators and target promoters that make up the circuit.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the instant case, the disclosure provides a detailed description a cascade genetic circuit

composed of the XylS2 transcriptional activator under the control of the NahR transcriptional activator, wherein both of the transcriptional activators are responsive to salicylate or other benzoate derivatives, and a *Pm* target promoter. This cascade genetic circuit is then reduced to practice in the Examples. Thus, the disclosure provides a detailed description of a single species of the claimed invention. However, this example is far from representative of the full scope of the claimed genus because the functional characteristics of the circuit, such as the identity of the inducer used, the cell type in which the circuit will function, the functionality of the circuit *in vitro*, which transcriptional regulators will function together and in what way, and which target sequence will function with any given set of transcriptional regulators, is dictated by the unique functional characteristics of the transcriptional regulators and target sequences making up the cascade genetic circuit.

As the application does not describe a representative number of species of the claimed invention, it is incumbent upon Applicant to disclose the relevant identifying characteristics of the genus of cascade genetic circuits encompassed by the claims in such clear and concise terms that the skilled artisan would recognize that Applicant was in possession of the full scope of the claimed invention at the time the instant application was filed. According to the Revised Interim Guidelines, identifying characteristics include, “structure or other physical and/or chemical properties,...functional characteristics coupled with a known or disclosed correlation between function and structure or... a combination of such identifying characteristics...” (Federal Register, Vol. 66, No. 4, page 1106, column 3, second full paragraph). The claims are generally directed to a circuit having the following characteristics: at least two transcriptional activators; at least one transcriptional activator under the control of another transcriptional activator; at least

two transcriptional activators under the control of an inducer; and a target promoter responsive to a transcriptional activator that is under the control of a second transcriptional activator. Beyond the single specific example set forth in the specification, the disclosure describes neither the structure nor the function of a cascade genetic circuit such that the skilled artisan could envision the correlation between function and structure. As the function of the cascade genetic circuit is highly dependent on the specific functional characteristics of the component parts of the cascade genetic circuit, a broad recitation of function does not adequately describe the circuit. For example, the function of a cascade genetic circuit would differ depending on whether one or more of the transcriptional regulators was an activator or repressor of transcription and, as already mentioned, the identity and functional characteristics of the inducer molecule will be different for different transcriptional regulators. In addition, the claims encompass cascade genetic circuits comprising three or more transcriptional regulators. The functional characteristics of a circuit having three, four, or five transcriptional regulators would surely be different from the example described in the specification, yet the disclosure is silent regarding how such a circuit would function. Thus the skilled artisan could not possibly envision the relevant identifying characteristics of the claimed genus of transcriptional regulators based on the teachings of the instant specification.

Claims 55-57 are additionally rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description for the genus of all transcriptional modulators “having the transcriptional modulating activity of” *nahR*, *Psal* or *XylS2*, and claim 58 is additionally rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate written description for the genus of all nucleic acid molecules having the promoter activity of *Pm*. The disclosure provides a single

example of each of the molecules having the activities set forth in the claim (i.e. *nahR*, *Psal*, *XylS2* and *Pm*) and provides no description of the relevant identifying characteristics of the molecules genus of molecules encompassed by the claims.

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of cascade genetic circuits encompassed by the claims and molecules having the function of *nahR*, *Psal*, *XylS2* or *Pm*. With respect to the method claims and claims to a host cell comprising the cascade genetic circuit, adequate description first requires an adequate description of the materials which provide the means for making or practicing the invention. Therefore, only the cascade genetic circuit reduced to practice in the disclosure meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 76 and 77 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 76 is indefinite in its recitation of “involved in” in the first line. It is unclear how the cascade genetic circuit is to be involved in the cell. For the purpose of examination on the

merits it is assumed that Applicant intends that the genetic circuit be “provided in” cultured eukaryotic cell and amending the claim accordingly would be remedial.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 48, 52-54, 60, 62-64, 67,68,70-73, 76-78 and 81 are rejected under 35 U.S.C. 102(b) as being anticipated by Aubrecht *et al.* (1996) *Gene* 172:227-231.

Aubrecht *et al.* teaches a cascade genetic circuit comprising: (a) an upstream transcriptional regulator (i.e. tetO) the expression of which stimulates expression of a downstream transcriptional regulator (i.e. LacI) wherein both tetO and LacI are responsive to an inducer (i.e. tetracycline and IPTG, respectively); (b) a target promoter responsive to the downstream transcriptional regulator (i.e. lacO); and (c) provided in a cultured eukaryotic cell (i.e. CHO; see especially Figure 1 and the caption thereto). Aubrecht *et al.* thus teaches all of the limitations of the cascade genetic circuit of claim 48 and the cell of claims 68. In addition, the cascade genetic circuit of Aubrecht *et al.* comprises two transcriptional regulators that are polypeptides according to claim 52 and encoded by exogenous nucleic acid molecules according to claims 53 and 54. In addition, the inducer of Aubrecht *et al.* modulates one of the transcriptional regulators that regulates the activity of the target promoter according to claim 60; the target promoter regulates the expression of a nucleic acid encoding a moiety of interest that is exogenous to a genome according to claims 62-64; and the circuit is provided in a cultured mammalian cell according to claims 67, 70 and 71.

Aubrecht *et al.* also teaches a method for expression of a nucleic acid molecule or making a moiety comprising: (a) establishing a cascade genetic circuit; (b) placing the nucleic acid molecule under the control of a target promoter; and (c) inducing the cascade genetic circuit according to claims 72 and 77 respectively (see especially Table 1 and the caption thereto). The method of Aubrecht *et al.* further comprises a nucleic acid molecule that encodes an enzyme (i.e. CAT) according to claims 73 and 78; and a cascade genetic circuit provided in a culture eukaryotic cell according to claims 76 and 81.

The cascade genetic circuit, cell comprising a cascade genetic circuit and method of using a cascade genetic circuit taught by Aubrecht *et al.* are the same as those taught in the instant application; therefore the limitations of the claims are met by Aubrecht *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

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January 22, 2003



JAMES KETTER
PRIMARY EXAMINER